



## Editorial

Ebola Virus: Understanding the 2014 Outbreak<sup>☆</sup>

## El virus del Ébola: comprendiendo el brote de 2014

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Ebola virus (EV) epidemics are not new to Africa. EV was first identified in 1976, the current one being the 25th known outbreak of EV infection.<sup>1,2</sup> As of November 28, a total of 16933 cases have been reported (10585 laboratory-confirmed), including 6002 deaths.<sup>3</sup> Reported cases are from countries with widespread transmission (16899 cases in Guinea, Liberia and Sierra Leone); countries with an initial case or limited transmission (4 cases in the US, 8 cases in Mali); and previously affected countries (1 in Senegal, 20 in Nigeria, 1 in Spain, where the outbreaks were declared over on 17 October, 19 October, and 2 December 2014, respectively). A national EV disease (EVD) outbreak is considered to be over when twice the 21-day incubation period (42 days) has elapsed since the last patient in isolation became laboratory-negative.

The clinical manifestations, illness duration, degree of transmissibility and mortality of EVD in the current epidemics do not differ from those in earlier epidemics. Thus the public health impact of the current outbreak is not due to the biological characteristics of the virus, but rather to a combination of social factors such as deficient health care systems, population mobility, local customs (e.g. traditional burials) and lack of international awareness.<sup>1,4</sup>

EVD is caused by infection with one of the Ebola virus strains that can cause disease in humans and nonhuman primates (monkeys, gorillas, and chimpanzees). Ebola viruses belong to the Filoviridae family, which are enveloped, nonsegmented, negative-strand RNA viruses and also include *Marburgvirus*, and “Cuevavirus”. Originally identified in 1976 in Yambuku, Zaire (now the Democratic Republic of Congo), and Nzara, South Sudan, EV (named after a river in Zaire) includes five separate species: *Zaire ebolavirus*, *Bundibugyo ebolavirus*, *Tai Forest ebolavirus*, *Sudan ebolavirus*, and *Reston ebolavirus*.<sup>5</sup> All known African EVs can infect humans and cause similar symptoms, but they vary in terms of disease progression and virulence. The strain causing the current epidemics in West

Africa bears 97% homology to the Zaire EV found in the Democratic Republic of Congo and Gabon.<sup>6</sup>

EVs are zoonotic pathogens thought to be carried by various species of fruit bats. Human introduction occurs through direct contact with bats or their excretions or secretions or through contact with other end hosts, such as the great apes. Outbreaks develop by human-to-human transmission started by a single introduction from the wildlife reservoir or another end host.<sup>7</sup> EV is spread mainly through contact with the body fluids of symptomatic patients or with objects that have been contaminated with the virus. Health-care providers, family and friends in close contact with Ebola patients, or persons in contact with infected wildlife (by handling bushmeat and by contact with infected bats) are at highest risk of becoming infected.

The incubation period typically lasts 5 to 7 days (ranging from 2 to 21 days). Polymerase chain reaction becomes positive usually 1 day before symptoms appear. EVD is characterized by nonspecific symptoms such as fever, fatigue, loss of appetite, vomiting, diarrhea, headache, and abdominal pain, as well as hemorrhage in less than half the cases.<sup>5,6</sup> The majority of patients are 15 to 44 years of age, half are male, and the case fatality rate is around 70%. Difficulty breathing was reported in 23% of cases.<sup>4</sup>

Once people recover from Ebola, they can no longer spread the virus to people in the community. Although Ebola virus has been detected in semen after patients have recovered, it is not known if the virus can be spread through sex. People who recover from Ebola infection develop antibodies that last for at least 10 years. It is not known if immunity lasts for life or if patients can become infected with a different EV species. Long-term complications, such as joint and vision problems, have been reported.<sup>3</sup>

Transmission can be stopped by a combination of early diagnosis and outbreak control measures.<sup>1,2</sup> Responding to cases involves isolation and treatment of patients, contact tracing, and monitoring each contact for 21 days. Attention to proper use of personal protection equipment (gown, glove, mask, eye protection, proper care while removing protection equipment) is of paramount importance.<sup>1,7</sup> Soap and water, alcohol-based hand sanitizers as well as dilute bleach inactivate the viral particles. Contacts need to be identified for monitoring daily temperature for 21 days and

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for isolation if they develop fever. At the local level, important preventive measures include: (i) early detection and isolation, as the greatest risk of transmission is not related to patients with diagnosed infection but to as yet unrecognized patients; (ii) education to modify local funeral practices to prevent contact with body fluids of people who have died from EVD, which is the second major form of propagation of the virus; (iii) avoidance of bush meat handling and contact with bats (which may be the primary reservoir of EV).

Supportive medical care (oxygen therapy, fluid resuscitation, treatment of other infections) can reduce case fatality rates substantially. Vaccines (cAd3-EBOV and rVSVΔG-EBOV-GP) are under study in humans. Both vaccine candidates have demonstrated 100% efficacy in studies in nonhuman primates.<sup>8</sup>

The therapeutic intervention closest to immediate release seems to be antibody treatment, which has been successful in macaques even when antibodies are administered more than 72 h after infection.<sup>9</sup> ZMapp is an experimental biopharmaceutical drug comprising 3 chimeric monoclonal antibodies under development as a treatment for EVD. The drug has not yet been subjected to a randomized controlled trial to determine its safety and efficacy.<sup>9</sup> Some patients have received hyperimmune serum from survivors of the disease but information regarding effectivity and potential side effects of this intervention is limited.

Other treatment approaches involve modulatory RNA (i.e., small interfering RNAs or phosphorodiamidate morpholino oligomers). TKM-Ebola (Tekmira Pharmaceuticals Corp. Vancouver, Canada) is a combination of small interfering RNA targeting 3 of the 7 proteins in EV (Zaire Ebola L polymerase, Zaire Ebola membrane-associated protein VP24, and Zaire Ebola polymerase complex protein VP35), formulated with Tekmira's lipid nanoparticle technology.<sup>10</sup> The FDA allows its use under expanded access in EV-infected patients.

AVI-7537 phosphorodiamidate morpholino oligomers targets EV protein VP24 through an RNA interference technology. This drug improved survival in nonhuman primates.<sup>11</sup> BCX-4430, an adenosine analogue, is active against EV in rodents and protected nonhuman primates from Marburg virus.<sup>12</sup> No human studies have been conducted. Other drugs approved for other indications have been proposed as treatment for EVD, such as chloroquine and

imatinib, which have shown activity against EV in vitro<sup>13</sup> and, in some cases, in rodent models.

In summary, unlike previous outbreaks, the current EV epidemics is characterized by (i) the large number of deaths caused; (ii) the involvement of the entire territory of 3 countries (Guinea, Liberia, Sierra Leone); (iii) the long duration (1 year to date); (iv) involvement of a territory (West Africa) previously unaffected by EVD; (v) the potential for this outbreak, unlike previous ones, to become endemic in West Africa, becoming a reservoir for spread of the virus to other areas of the world.<sup>1,2</sup> A better understanding of disease transmission and mechanisms will help effective outbreak control and individual patient treatment.

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